Hematopoietic Stem Cell Transplantation (HSCT) using Umbilical Cord Blood Units (UCB) Not Depleted of Red Blood Cells Prior to Cryopreservation.

Robert Chow, MD, AM[1,8], Auayporn Nademanee, MD[2], Joseph Rosenthal, MD[2], Chatchada Karanes, MD[2], Tang-Her Jaing, MD[3], Patrick Tan, MD[4], Michael Graham, MD[5], Brian Wang, BS[6], David Gjertson, PhD[6,7] and Lawrence Petz, MD[1,7]. [1]StemCyte International Cord Blood Center, Arcadia, CA and Taiwan, [2]City of Hope National Medical Center, Duarte, CA, [3]Chung Gung Memorial Hospital, Linko, Taiwan, [4]Mount Elizabeth Hospital, Singapore, [5]Univ. of Arizona Medical Center, Tuscon, AZ, [6]Department of Biostatistics, UCLA School of Public Health, Los Angeles, CA, USA, [7]UCLA Medical Center, Los Angeles, CA, [8]StemCyte Research Institute, Los Angeles, CA

STEMCYTE

ABSTRACT

UCB is an attractive source for HSCT; however, limiting cell dose has hampered its widespread use. The red cell depletion (RD) techniques that are widely used incur significant nucleated cell loss after processing. One method of minimizing cell loss during processing is to deplete plasma (PD) but not red blood cells. A large racially diverse inventory of over 22,000 PD UCB is now available on stem cell registries; however, clinical outcome for HSCT using PD UCB products is unavailable. A retrospective analysis of all patients with engraftment or survival data up to April 2005 was performed on 118 HSCT using PD UCB ("All"). When patients with prior transplants or transplanted during relapse were excluded in the engraftment and survival analysis ("Remission Patients"), the total was 98. Average loss of less than 0.1% nucleated cells was found in the discarded plasma fraction after PD UCB processing (n=27), though clumping limited the cellular fraction recovery to 90%. The characteristics for the 118 transplants were: median age 8 yo, range 0.3-55, 31 >16 yo (26%); median weight 26 kg, range 4.5-103, 36 >50kg (31%); male 61%; median # HLA ABDR matches 4.0; median pre-freeze TNC dose 5.6 x 10^7/kg (n=118); transplant center reported median post-thaw TNC dose 5.2 x 10^7/kg (n=68); median pre-freeze CD34 dose 1.8 x 10^5/kg; malignant indications 75%; transplants outside U.S. 35%; double transplant 16%; and non-myeloablative 8%. For all patients, the median time to engraftment for ANC 500 (n=87), platelet 20K (n=72) and 50K (n=68) were 22.0 days (range 7-64), 49.5 days (range 13-95), and 58.5 days (range 21-132) respectively. Unadjusted cumulative incidence of ANC500 and platelet 20K and 50K engraftment were 90±3%, 77±5% and 75±5% respectively for 118 patients, and 94±3%, 81±5% and 80±5% respectively for the 98 remission patients. The incidence of grade III-IV acute GVHD and extensive chronic GVHD were 15% and 13% respectively. Relapse rate for malignancies were 25±6% for all patients (n=85) and 20±6% for remission patients (n=70), and TRM were 26±4% (n=118) and 20±4% (n=98) respectively for the two groups at 1 year. With a median follow-up of 526 days (range 106-1,284 days) for the surviving patients, the Kaplan-Meier estimates of 1-year OS (n=118) and DFS (n=86) are 65±5% and 50±7% respectively for all patients, and 73±5% (n=98) and 59±6% (n=70) respectively for the remission patients. These results demonstrate that HSCT using PD UCB can be performed safely and effectively.

INTRODUCTION

One method of minimizing cell loss during processing is to deplete plasma (PD) but not red blood cells. A large racially diverse inventory of over 18,000 PD UCB is now available on stem cell registries; however, clinical outcome for HSCT using PD UCB products is unavailable. A retrospective analysis of all patients with engraftment or survival data up to April 2005 was performed on 118 HSCT using PD UCB ("All"). The subsets of (1) first transplant patients in remission, (2) benign indications, (3) malignant indications, (4) NMDP faciliated vs. non-NMDP facilitated US and Taiwan transplants, (5) pediatric weight patients (<50kg), (6) adult weight patients (>50kg), (7) single unit transplants, and (8) transplants with post-thaw washed vs. unwashed units were also studied.

STUDY DESIGN

- Inclusion Criteria – All transplants between Nov 2001 and Apr 2005. = 162
- Data Supplied & Audited by NMDP & Transplant Ctrs. #CBT Data Not Avail. = 44 (27%)
- "All Patients" Engraftment or Survival Data available for 118 of 162 transplanted – 73%
- Data available for 58 out of 64 NMDP transplants – 91%
- 89/117 US transplants - 76% 29/45 Taiwan transplants - 64%
- "Relapse/Re-transplant" Transplants (Prior Transplant and/or Transplanted during Relapse) = 20
- "Remission/1st Transplant" Patients = 98 (Remission patients without prior transplants)
- Single Cords = 99 Double UCB Transplants = 19 Non-Myeloablative = 7 1 UCB/haploidentical PSCT

AUDITS & STATISTICS

1. 58/118 or 49% patient data audited & supplied by NMDP and re-audited by Transplant Centers; remainder audited & supplied by Transplant Centers
2. Kaplan-Meier estimates for probabilities of overall survival
3. Unadjusted Cumulative Incidence for engraftment (Patients who expired before engraftment as graft failures)

Patient Characteristics (n=118)

- Sex: M 72 (61%) F 56 (39%)

	Average	Median	Range
Age			
31 transplants in patients over age 16 (26%)	14	8	0.3-55
Weight			
36 transplants in patients over 50 kg (31%)	36	26	4.5 – 103

Disease Characteristics (n=118)

- Benign = 29 (25%); Hemoglobinopathies 14, AA 6, WAS 5, SCID 2, Others 2 (25%)
- Malignant = 89 (75%); ALL 37, AML 22, CML 9, Other 21
- #1CR/1CP = 20 transplants (22% of malignant)
- #Relapse/Re-Transplant = 20 transplants (22% of malignant)
- #In relapse, induction failure, resistant, blast crisis =16 # Prior Transplants = 7

CBU Characteristics (n=118)

TNC Dose/Kg	Pre-Freeze (n=118)	TC reported Post-Thaw (n=68)	
Average	7.6 x 10^7	7.9 x 10^7	100% Recovery
Median	5.6 x 10^7	5.2 x 10^7	93% Recovery

CD34 Dose/Kg Pre-Freeze (n=117)

- Average 2.6 x 10^5 Median 1.8 x 10^5

Median Post-Thaw Viability (Per TC) 75.0% Median #HLA ABDR Matches 4.0

Source Cord Blood Bank & Transplant Centers

StemCyte U.S. – 89 (75% with 58 NMDP & 31 Non-NMDP); StemCyte Taiwan – 29 (25%)

U.S. – 77 Transplants (65%); Foreign – 41 Transplants (35%)

Post-Thaw Washed vs. Unwashed Analysis:

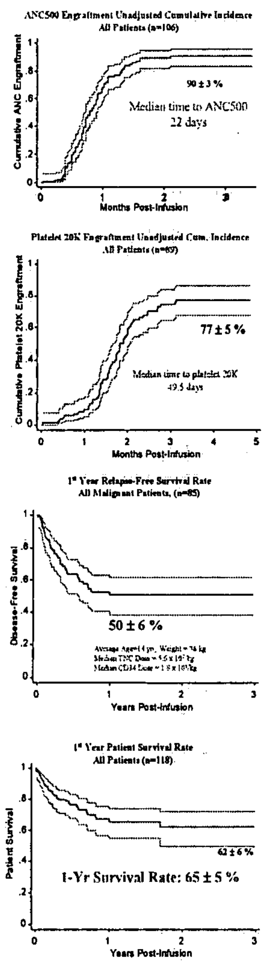
Washed – 43 Transplants; Unwashed – 40 Transplants

Adjusted via Cox Regression for malignancy, TNC dose, single vs. double cord TX, HLA matches, recipient sex, age and high risk status

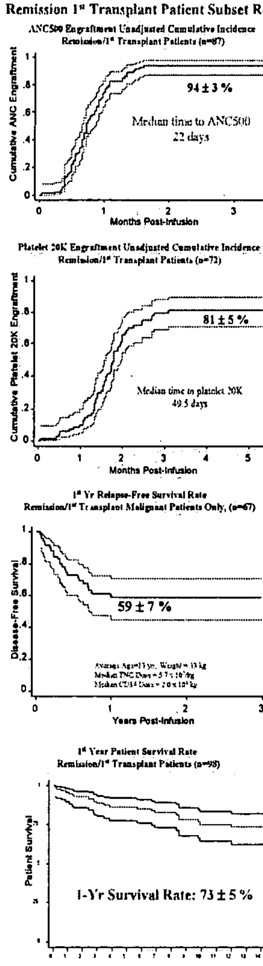
SUMMARY OF RESULTS

	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Median #Days to ANC 500 Engraftment Unadjusted Cumulative Incidence*	22 days 90 ± 3 %	22 days 94 ± 3 %	22 days 94 ± 3 %	21 days [illegible]	22 days [illegible]	24 days [illegible]	17.5 days [illegible]	14 days [illegible]
Median #Days to Plt 20K Engraftment Unadjusted Cumulative Incidence*	50 days 77 ± 5 %	55 days 79 ± 6 %	50 days 81 ± 5 %	50 days [illegible]	[illegible]	52 days 72±6%	47 days 89±7%	47 days [illegible]
Median #Days to Plt 50K Engraftment Unadjusted Cumulative Incidence*	59 days 75 ± 5%	63 days 78 ± 6 %	58 days 80 ± 5 %	58 days [illegible]	[illegible]	63 days [illegible]	55 days [illegible]	55 days [illegible]
1-Yr Relapse Rate (Malignant Cases)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	NA	NA
1-Yr Overall Survival (K-M)	65±5%	62±7%	73±5%	[illegible]	[illegible]	[illegible]	[illegible]	[illegible] (OS)

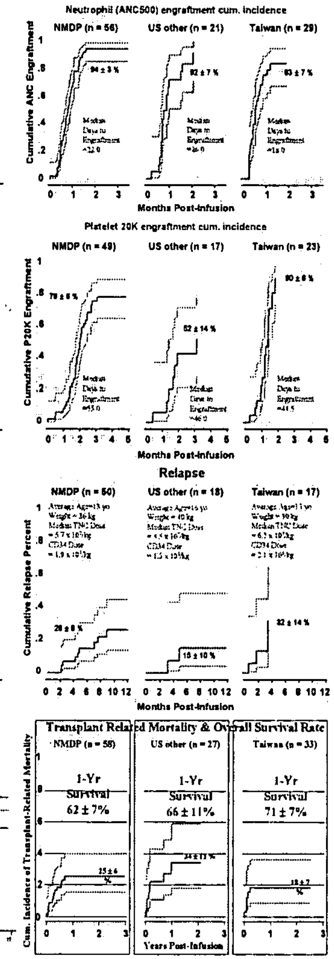
Overall Patient Results



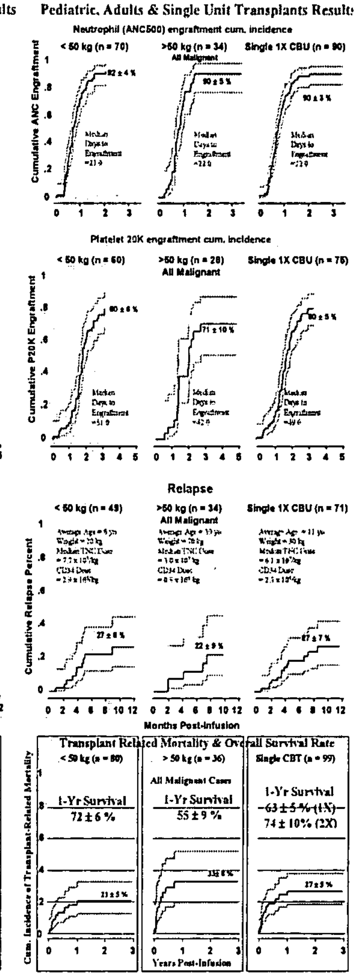
Remission 1st Transplant Patient Subset Results



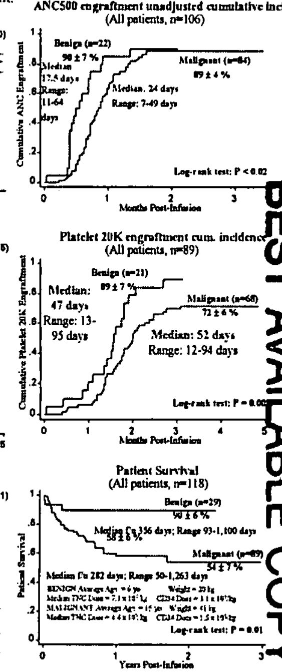
NMDP, Non-NMDP US & Taiwan Subset Results



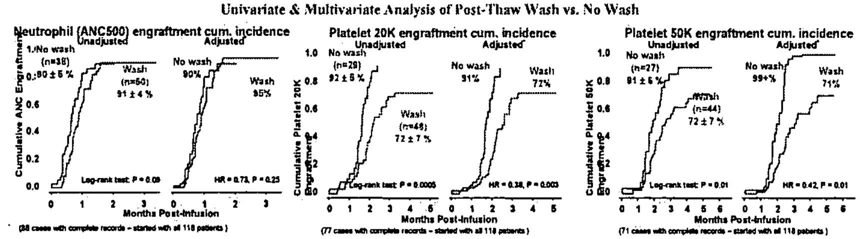
Pediatric, Adults & Single Unit Transplants Results



Benign & Malignant Indication Results



Univariate & Multivariate Analysis of Post-Thaw Wash vs. No Wash



Alternative Explanations Ruled Out

- •NMDP data >90% complete, precluding significant favorable reporting bias. Non-NMDP data is similar to non-NMDP data
- •Contribution by Second CBU from another bank in double transplant
- •Better HLA match as the explanation
- •Better Patients as explanation: Patient Characteristics, Malignancy Rate, Advanced Disease Status similar to other banks

Differences:

- •Higher TNC Dose for StemCyte PD Transplants
- •Worse HLA Matches for StemCyte Transplants
- •StemCyte has higher minority transplants
- •StemCyte has higher % foreign transplants.

Preliminary Conclusions-Plasma Depleted & Non-Red Cell Depleted (PD) Cord Blood Units

- •Largest and only patient outcome series for PD CBU.
- •On average, PD UCB transplants have higher average & median cell dose.
- •Unadjusted cumulative incidence of neutrophil and platelet engraftment appear to be significantly better than red cell depleted (RD) units for children & adults – perhaps related to higher cell dose of PD UCB transplants.
- •Outstanding speed of neutrophil and platelet engraftment, approaching that of bone marrow transplants for benign indications – perhaps related to higher cell dose.
- •Outstanding 1-year survival rate and transplant-related mortality rate appear to be significantly improved versus RD units for adults and children, especially benign indications.
- •Relapse rate similar to RD UCB transplants.
- •Not washing post-thaw appears to improve engraftment significantly vs washing for PD units.
- •Matched pair analysis vs. red cell depleted CBU transplants or prospective trials are needed to confirm these preliminary observations.

References

Alonso et al. Cytotherapy (2001) 3: 429; Barker et al. NEJM (2001) 344:1870; Barker et al. Blood (2005) 105:1343; Escolar et al. NEJM (2005) 352:2069-81; Fang et al. J. Hemat Oncol (2004) 26:185; Hall et al. J. Hemat Oncol (2004) 26:382; Hung et al. Int. J. of Hematology (2005) 82: ; Jaing et al. J. Trop. Ped (2005)51:122; Jaing et al. BBMT (2005)11:349; Kurtzberg et al. NEJM (1996) 335:157; Gluckman et al. NEJM (1989) 321:1174; Gluckman et al. NEJM (1997) 337:373; Laughlin et al. NEJM (2001) 344:1815; Laughlin et al. NEJM (2004) 351:2265; Rocha et al. Blood (2001) 97:2962; Rocha et al. NEJM (2004) 351:2276-85; Rubinstein et al. PNAS (1995) 92:10119;Rubinstein et al. NEJM (1998) 339:1585; Takahashi et al. Blood (2004) 104:3813; Tan et al. Am J. Hemat (2004) 75:209, Wagner et al. Lancet (1995) 346:214, Wagner et al. Blood (2002) 100:1611

EXHIBIT B

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Post-Thaw Washed vs. Unwashed Analysis:

Washed – 43 Transplants; **Unwashed – 40 Transplants**

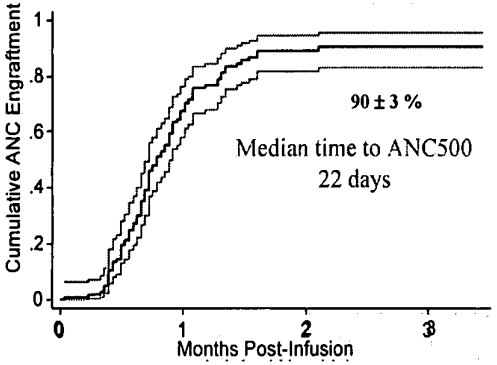
Adjusted via Cox Regression for malignancy, TNC dose, single vs. double cord TX, HLA matches, recipient sex, age and high risk status

SUMMARY OF RESULTS

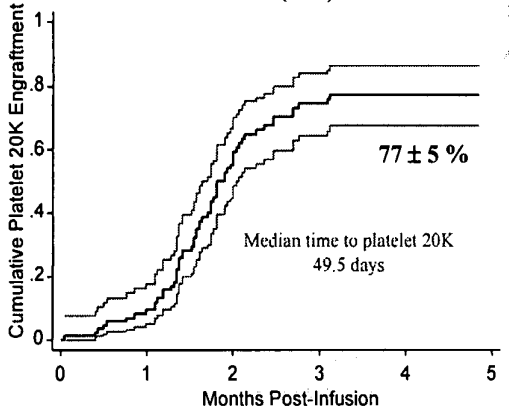
	ALL PATIENTS (n=118)	NMDP Audited Transplants (n=58)	Remission 1 " Transplant (n=98)	Pediatric <50Kg (n=80)	Adult >50Kg (n=36; all malignant)	Malignant Indications " (n=89)	Benign Indications " (n=29)	Thalassemia Chung Gung (n=10)
Median #Days to ANC 500 Engraftment Unadjusted Cumulative Incidence*	22 days 90 ± 3 %	22 days 94 ± 3 %	22 days 94 ± 3 %	21 days 92±4%	22 days 90±5%	24 days 89±4%	17.5 days 90±7%	14 days 90%
Median #Days to Plt 20K Engraftment Unadjusted Cumulative Incidence*	50 days 77 ± 5 %	55 days 78 ± 6 %	50 days 81 ± 5 %	50 days 80±6%	49 days 71 ± 10%	52 days 72±6%	47 days 89±7%	47 days 90%
Median #Days to Plt 50K Engraftment Unadjusted Cumulative Incidence*	58 days 75 ± 5%	63 days 78 ± 6 %	58 days 80 ± 5 %	58 days 78±6%	61 days 69 ± 11%	63 days 70±3%	55 days 87±8%	55 days 90%
1-Yr Relapse Rate (Malignant Cases)	25±6%	26±8%	19±6%	27±8%	22±9%	25±6%	NA	NA
1-Yr Overall Survival (K-M)	65±5%	62±7%	73±5%	72±6%	55±9%	58±6%	90±6%	90% (OS)

Overall Patient Results

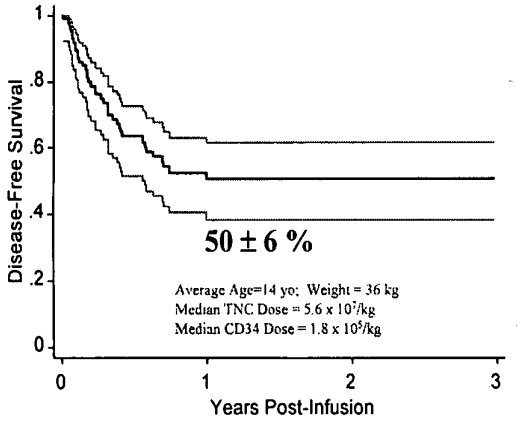
ANC500 Engraftment Unadjusted Cumulative Incidence
All Patients (n=106)



Platelet 20K Engraftment Unadjusted Cum. Incidence
All Patients (n=89)

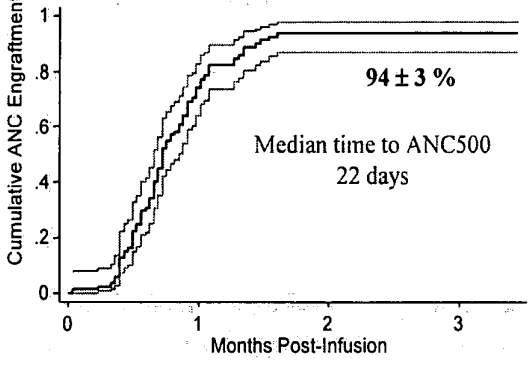


1st Year Relapse-Free Survival Rate
All Malignant Patients, (n=85)

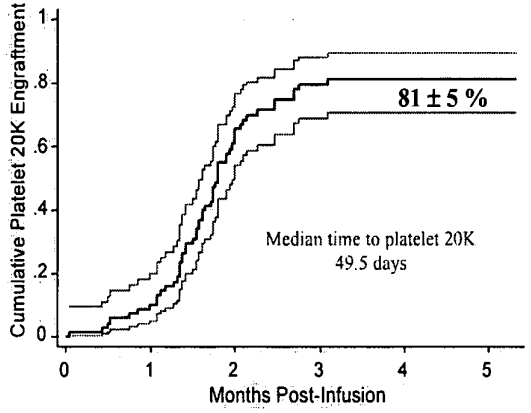


Remission 1st Transplant Patient Subset Results

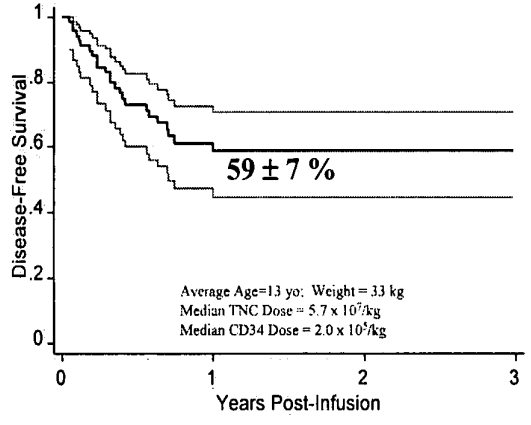
ANC500 Engraftment Unadjusted Cumulative Incidence
Remission/1st Transplant Patients (n=87)



Platelet 20K Engraftment Unadjusted Cumulative Incidence
Remission/1st Transplant Patients (n=72)

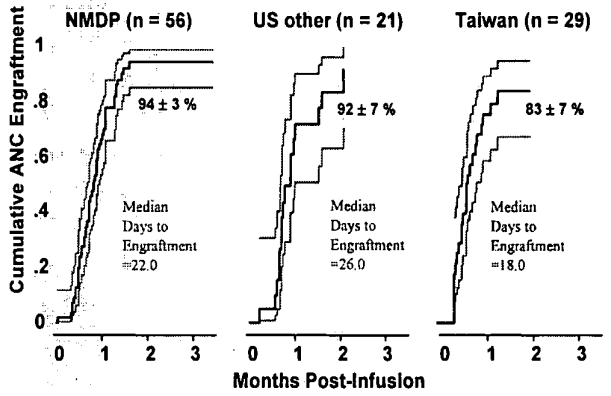


1st Yr Relapse-Free Survival Rate
Remission/1st Transplant Malignant Patients Only, (n=67)

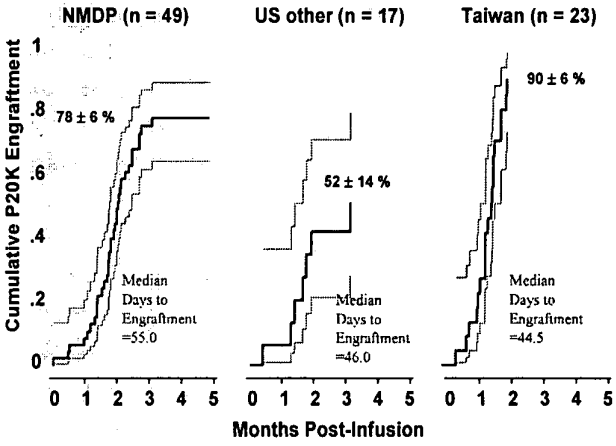


NMDP, Non-NMDP US & Taiwan Subset Results

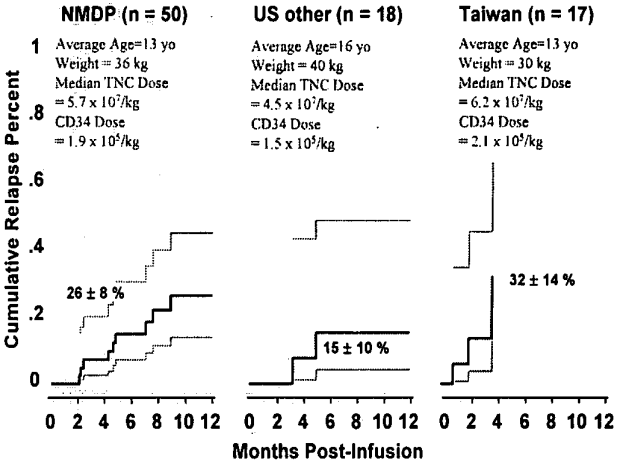
Neutrophil (ANC500) engraftment cum. incidence

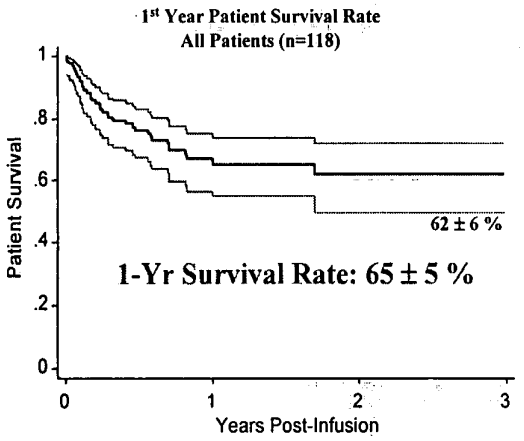


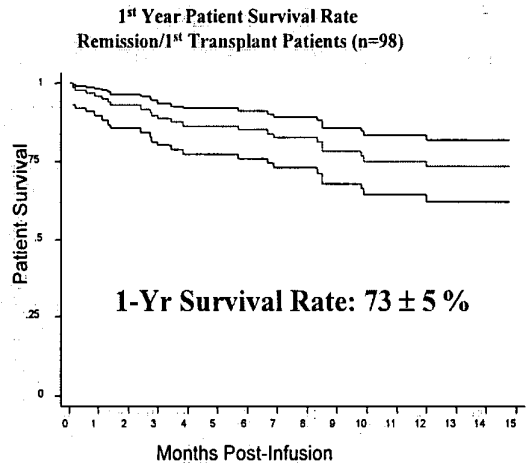
Platelet 20K engraftment cum. incidence

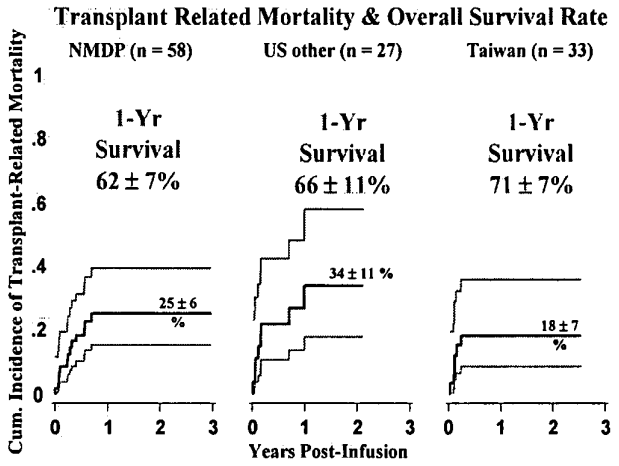


Relapse

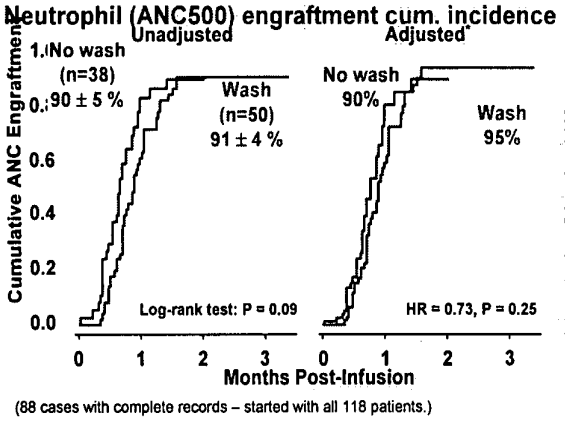




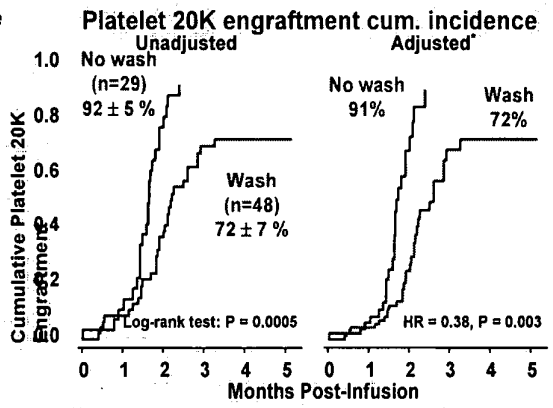




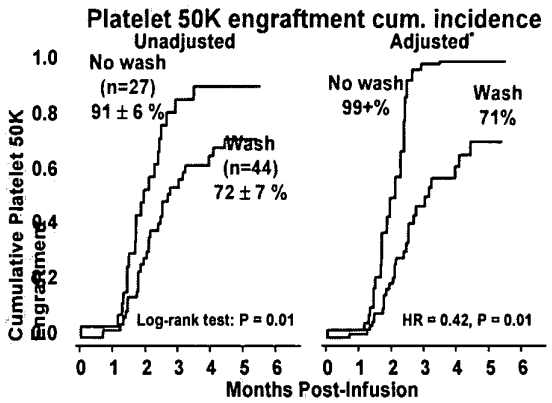
Univariate & Multivariate Analysis of Post-Thaw Wash vs. No Wash



(88 cases with complete records – started with all 118 patients.)



(77 cases with complete records – started with all 118 patients.)

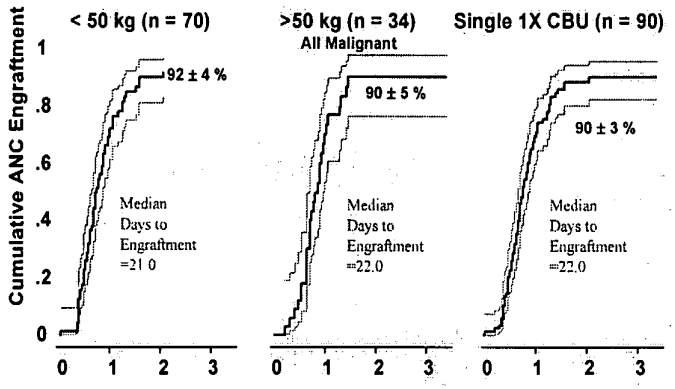


(71 cases with complete records – started with all 118 patients.)

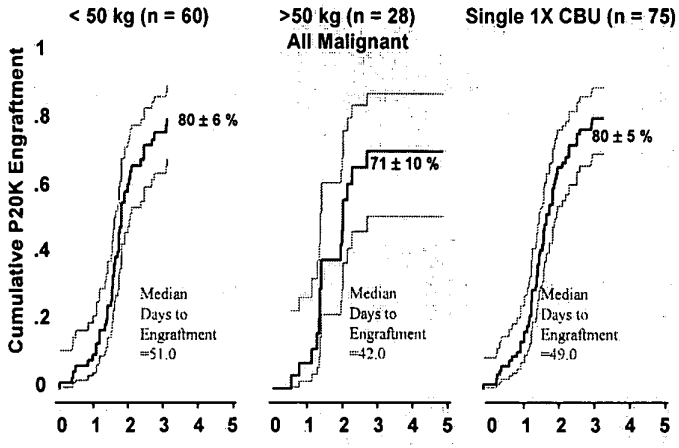
Angeles, CA

Pediatric, Adults & Single Unit Transplants Results

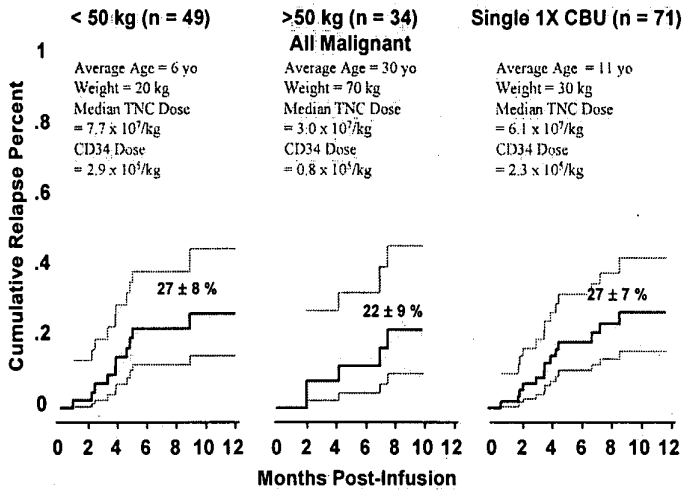
Neutrophil (ANC500) engraftment cum. incidence



Platelet 20K engraftment cum. incidence

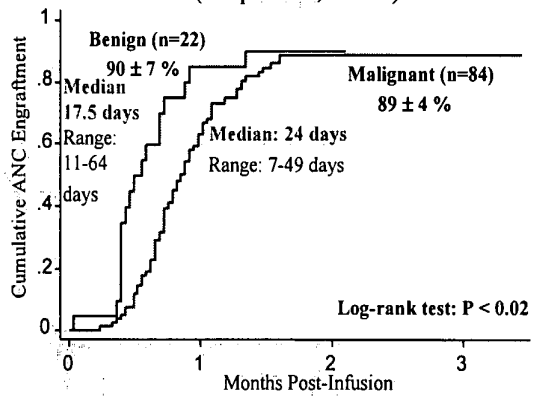


Relapse

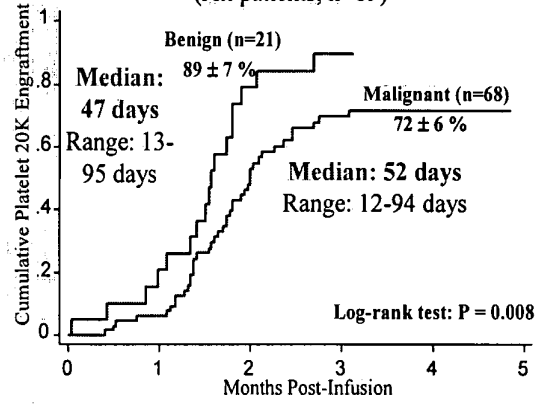


Benign & Malignant Indication Results

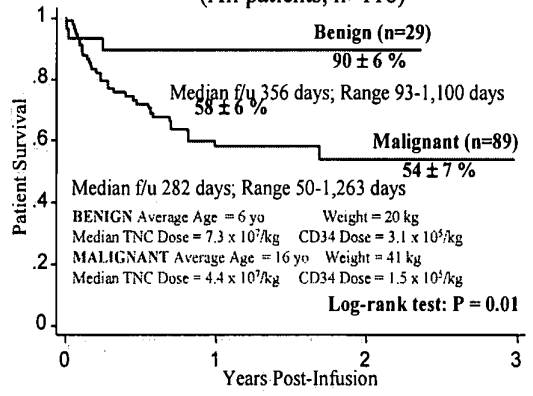
ANC500 engraftment unadjusted cumulative incidence
(All patients, n=106)



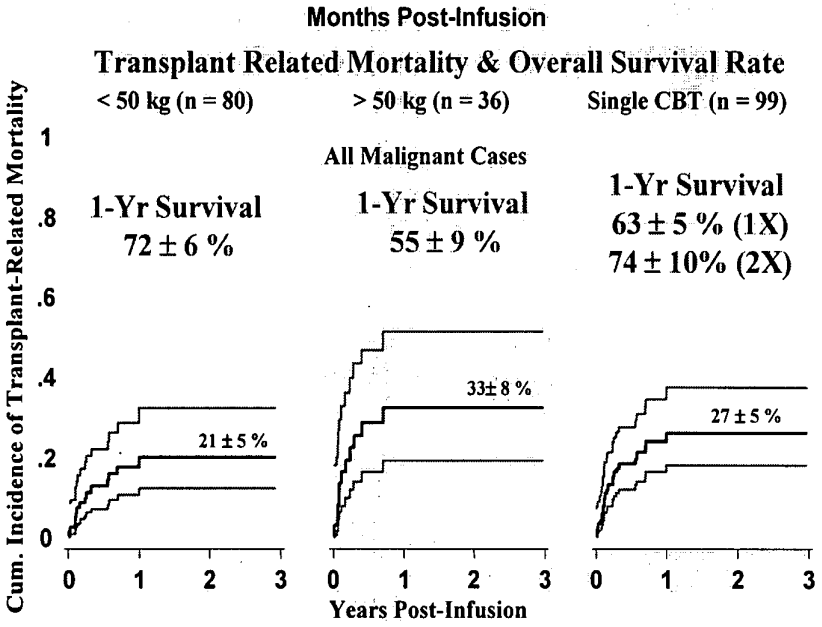
Platelet 20K engraftment cum. incidence
(All patients, n=89)



Patient Survival
(All patients, n=118)



Preliminary Conclusions-Plasma Depleted & Non-Red



Alternative Explanations Ruled Out

•NMDP data >90% complete, precluding significant favorable reporting bias. Non-NMDP data is similar to non-NMDP data

•Contribution by Second CBU from another bank in double transplant

•Better HLA match as the explanation

•Better Patients as explanation: Patient Characteristics, Malignancy Rate, Advanced Disease Status similar to other banks

Differences:

•Higher TNC Dose for StemCyte PD Transplants

•Worse HLA Matches for StemCyte Transplants

•StemCyte has higher minority transplants

•StemCyte has higher % foreign transplants.

Preliminary Conclusions-Plasma Depleted & Non-Red Cell Depleted (PD) Cord Blood Units

•Largest and only patient outcome series for PD CBU.

•On average, PD UCB transplants have higher average & median cell dose.

•Unadjusted cumulative incidence of neutrophil and platelet engraftment appear to be significantly better than red cell depleted (RD) units for children & adults – perhaps related to higher cell dose of PD UCB transplants.

•Outstanding speed of neutrophil and platelet engraftment, approaching that of bone marrow transplants for benign indications – perhaps related to higher cell dose.

•Outstanding 1-year survival rate and transplant-related mortality rate appear to be significantly improved versus RD units for adults and children, especially benign indications.

•Relapse rate similar to RD UCB transplants.

•Not washing post-thaw appears to improve engraftment significantly vs washing for PD units.

•Matched pair analysis vs. red cell depleted CBU transplants or prospective trials are needed to confirm these preliminary observations.

References

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